The First Enantioselective Organocatalytic Mukaiyama-Michael Reaction. A Direct Method for the Synthesis of Enantioenriched γ-Butenolide Architecture.

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Supporting Information

General Information. Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[1] Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chloroform was distilled from calcium hydride prior to use. Chromatographic purification of products was accomplished using forced-flow chromatography on ICN 60 32-64 mesh silica gel 63 according to the method of Still.[2] Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching or anisaldehyde stain.

^{1}H and ^{13}C NMR spectra were recorded on Varian Mercury 300 (300 MHz and 75 MHz respectively) as noted, and are internally referenced to residual protio solvent signals. Data for ^{1}H are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz) and assignment. Data for ^{13}C NMR are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the California Institute of Technology Mass Spectral facility. Gas liquid chromatography (GLC) was performed on Hewlett-Packard 6850 and 6890 Series gas chromatographs equipped with a split-mode capillary injection system and flame ionization detectors using a Bodman

Chiraldex β-DM or Γ-TA (30 m x 0.25 mm) column. High performance liquid chromatography (HPLC) was performed on Hewlett-Packard 1100 Series chromatographs using Chiralcel AD column (1.6 x 25 cm) and AD guard (1.6 x 5 cm), Chiralcel OD–H (1.6 x 25 cm) and OD guard (1.6 x 5 cm), or Chiralcel AS (1.6 x 25 cm) and AS guard (1.6 x 5 cm) as noted.

Trimethyl-(5-ethyl-furan-2-yloxy)-silane. To a round bottom flask equipped with a magnetic stir bar and charged with CH_2Cl_2 (50 mL) was added 5-ethyl-5*H*-furan-2-one[3] (6.5 g, 58 mmol) and triethylamine (11 mL, 81 mmol), which was cooled to 0 °C. Trimethylsilyl trifluoromethanesulfonate (12 mL, 64 mmol) was added slowly and allowed to stir at room temperature for 6 hours. The reaction mixture was concentrated *in vacuo* and the top layer was decanted and purified by distillation (14 mmHg, 94 °C) to provide the title compound as a pale yellow oil (7.6 g, 71% yield).

(3,5-Dimethyl-furan-2-yloxy)-trimethyl-silane. To a round bottom flask equipped with a magnetic stir bar and charged with CH_2Cl_2 (5 mL) was added 3,5-dimethyl-3*H*-furan-2-one[4] (0.56 g, 5.0 mmol) and triethylamine (0.97 mL, 7.0 mmol), which was cooled to 0 °C. Trimethylsilyl trifluoromethanesulfonate (0.99 mL, 5.5 mmol) was added slowly and allowed to stir at room temperature for 6 hours. The reaction mixture was concentrated *in vacuo* and the top layer was decanted and purified by distillation (40 mmHg, 85 °C) to provide the title compound as a colorless oil (0.62 g, 68% yield).

General Procedure: To a 2-dram vial equipped with a magnetic stir bar and charged with (*2S*, *5S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one was added solvent, 2,4-dinitrobenzoic acid and aldehyde, then placed in a bath at the appropriate

temperature. The solution was stirred for 10 min before the addition of the siloxy-furan substrate in one portion. The resulting solution was stirred at constant temperature until reaction was determined to be complete by GLC conversion assay using dibenzyl ether as an internal standard. The reaction mixture was then transferred cold through a silica gel plug with ether into a flask and carefully concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (solvents noted) and fractions carefully concentrated *in vacuo* to provide the title compounds. The enantioselectivity was determined by chiral GLC analysis.

(*3R, 2'R*)-3-(2'-Methyl-5'-oxo-2', 5'-dihydro-furan-2'-yl)-butyraldehyde (Table 2, Entry 1). Prepared according to the general procedure from (*E*)-crotonaldehyde (166 μL, 2.00 mmol), trimethyl-(5-methyl-furan-2-yloxy)-silane (184 μL, 1.00 mmol), (*2S, 5S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (49.2 mg, 0.200 mmol), 2,4-dinitrobenzoic acid (42.4 mg, 0.20 mmol), H_2O (36.0 μL, 2.00 mmol), and CH_2Cl_2 (4.0 mL) at −70 °C for 11 h to provide the title compound as a colorless oil (135.5 mg, 81% yield, 22 : 1 dr, 92% ee) after silica gel chromatography (40% EtOAc/ hexanes). IR (film) 3082, 2968, 2729, 1752, 1721, 1379, 1249, 1119, 948.1, 818.4 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.75 (s, 1H, CHO), 7.38 (d, *J* = 5.5 Hz, 1H, C**H**CHCO$_2$), 6.09 (d, *J* = 5.5 Hz, 1H, CHC**H**CO$_2$), 2.66- 2.52 (m, 2H, MeCH, C**H**$_2$), 1.97- 1.82 (ddd, *J* = 2.2, 9.9, 18.7 Hz, 1H, C**H**$_2$), 1.47 (s, 3H, OCCH$_3$); 0.99 (d, *J* = 7.1 Hz, 3H, CHC**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.5, 158.7, 121.8, 100.2, 90.7, 46.0, 35.0, 23.2, 16.2; HRMS (CI) exact mass calcd for ($C_9H_{12}O_3$) requires *m/z* 168.0786, found *m/z* 168.0781. $[\alpha]_D$ = + 46 9 (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by GLC using a Bodman Chiraldex Γ-TA (30 m x 0.25 mm) column (100 °C isotherm for 7 min then 160 °C isotherm , 1 mL/min); (*3S, 2'S*) isomer t_r = 22.8 min and (*3R, 2'R*) isomer t_r = 23.8 min.

(*3R, 2'R*)-3-(2'-Methyl-5'-oxo-2', 5'-dihydro-furan-2'-yl)-hexanal (Table 2, Entry 2). Prepared according to the general procedure from (*E*)-hexenal (348 μL, 3.00 mmol), trimethyl-(5-methyl-furan-2-yloxy)-silane (184 μL, 1.00 mmol), (*2S, 5S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (49.2 mg, 0.200 mmol), 2,4-dinitrobenzoic acid (42.4 mg, 0.20 mmol), H_2O (36.0 μL, 2.00 mmol), and CH_2Cl_2 (4.0 mL) at −50 °C for 20 h to provide the title compound as a colorless oil (170.0 mg, 87% yield, 31 : 1 dr, 84% ee) after silica gel chromatography (40% EtOAc/hexanes). IR (film) 3093, 2960, 2863, 2722, 1757, 1722, 1602, 1455, 1380, 1286, 1247, 1198, 1119, 1094, 1034, 951.8, 821.8 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.57 (t, *J* = 1.6 Hz, 1H, CHO), 7.31 (d, *J* = 5.5 Hz, 1H, C**H**CHCO$_2$), 5.92 (d, *J* = 5.5 Hz, 1H, CHC**H**CO$_2$), 2.36- 2.14 (m, 3H, C**H**C**H$_2$**CHO), 1.38- 0.98 (m, 4H, C**H$_2$**C**H$_2$**), 1.32 (s, 3H, OCCH$_3$); 0.74 (t, *J* = 7.1 Hz, 3H, CH$_2$C**H$_3$**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.8, 171.9, 159.4, 121.5, 91.0, 44.1, 30.0, 33.0, 23.2, 21.2, 14.3; HRMS (CI) exact mass calcd for ($C_{11}H_{16}O_3$) requires *m/z* 196.1100, found *m/z* 196.1093. $[\alpha]_D$ = + 21.1 (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by GLC using a Bodman Chiraldex Γ-TA (30 m x 0.25 mm) column (170 °C isotherm, 1 mL/min); (*3S, 2'S*) isomer t_r = 13.4 min and (*3R, 2'R*) isomer t_r = 14.7 min.

(*3S, 2'R*)-4-Methyl-3-(2'-methyl-5'-oxo-2', 5'-dihydro-furan-2'-yl)-pentanal (Table 2, Entry 3). Prepared according to the general procedure from (*E*)-4-methyl-2-pentenal (350 μL, 3.00 mmol), trimethyl-(5-methyl-furan-2-yloxy)-silane (184 μL, 1.00 mmol), (*2S, 5S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (49.2 mg, 0.200 mmol), 2,4-dinitrobenzoic acid (42.4 mg, 0.20 mmol), H_2O (36.0 μL, 2.00 mmol), and toluene (4.0 mL) at −20 °C for 30 h to provide the title compound as a colorless oil (156.1 mg, 80% yield, 7 : 1 dr, 98% ee) after silica gel chromatography (40% EtOAc/

hexanes). IR (film) 3093, 2963, 2874, 2722, 1758, 1723, 1602, 1467, 1389, 1371, 1260, 1236, 1115, 1088, 1040, 953.0, 822.4 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.60 (t, *J* = 1.6 Hz, 1H, CHO), 7.31 (d, *J* = 5.5 Hz, 1H, C**H**CHCO$_2$), 5.92 (d, *J* = 5.5 Hz, 1H, CHC**H**CO$_2$), 2.43 (ddd, *J* = 2.7, 6.0, 8.8 Hz, 1H, CHC**H**CH$_2$), 2.24 (dd, , *J* = 1.6, 6.0, 8.8 Hz, 2H, C**H$_2$**), 1.88-1.74 (m, 1H, C**H**(CH$_3$)$_2$), 1.30 (s, 3H, OCCH$_3$); 0.78 (s, *J* = 7.1 Hz, 3H, CH(C**H$_3$**)$_2$); 0.64 (s, *J* = 7.1 Hz, 3H, CH(C**H$_3$**)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.1, 171.9, 159.8, 121.3, 91.8, 44.7, 39.5, 28.1, 24.5, 23.3, 17.9; HRMS (EI) exact mass calcd for ($C_{11}H_{16}O_3$) requires *m/z* 196.1099, found *m/z* 196.1093. $[\alpha]_D$ = + 12.8 (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by GLC using a Bodman Chiraldex Γ-TA (30 m x 0.25 mm) column (170 °C isotherm, 1 mL/min); (*3S*, *2'S*) isomer t_r = 12.2 min and (*3R*, *2'R*) isomer t_r = 13.8 min.

(*3S*, *2'R*)-3-(2'-methyl-5'-oxo-2', 5'-dihydro-furan-2'-yl)-3-phenyl-propionaldehyde (Table 2, Entry 4). Prepared according to the general procedure from (*E*)-cinnamaldehyde (378 μL, 3.00 mmol), trimethyl-(5-methyl-furan-2-yloxy)-silane (184 μL, 1.00 mmol), (*2S*, *5S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (49.2 mg, 0.200 mmol), 2,4-dinitrobenzoic acid (42.4 mg, 0.20 mmol), H_2O (36.0 μL, 2.00 mmol), and trichloroethylene (4.0 mL) at −40 °C for 30 h to provide the title compound as a colorless oil (177.1 mg, 77% yield, 6 : 1 dr, 99% ee) after silica gel chromatography (40% EtOAc/hexanes). IR (film) 2831, 2722, 1757, 1723, 1602, 1602, 1493, 1454, 1378, 1226, 1106, 953.2, 820.7 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.47 (s, 1H, CHO), 7.34-7.16 (m, 5H, C$_5$**H$_5$**), 7.31 (d, *J* = 6.0 Hz, 1H, C**H**CHCO$_2$), 5.98 (d, *J* = 5.5 Hz, 1H, CHC**H**CO$_2$), 3.50 (dd, , *J* = 5.5, 8.2 Hz, 3H, C**H**Ph), 2.84 (ddd, *J* = 1.6, 8.8, 18.1 Hz, 1H, C**H**$_2$CHO), 2.84 (ddd, *J* = 1.1, 5.5, 18.1 Hz, 1H, C**H**$_2$CHO), 1.22 (s, 3H, OCCH$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.0, 172.3, 161.0, 138.4, 129.5, 128.8, 127.9, 120.9, 90.2, 46.1, 44.7, 22.4; HRMS (CI) exact mass calcd for ($C_{14}H_{14}O_3$) requires *m/z* 230.0943,

found *m/z* 230.0934. $[\alpha]_D$ = + 69.7 (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by GLC using a Bodman Chiraldex Γ-TA (30 m x 0.25 mm) column (170 °C isotherm, 1 mL/min); (*3R, 2'R*) isomer t_r = 61.7 min and (*3S, 2'S*) isomer t_r = 64.0 min.

(*2S, 2'R*)-Benzoic acid 2-(2'-methyl-5'-oxo-2', 5'-dihydro-furan-2'-yl)-4-oxo-butyl ester (Table 2, Entry 5). Prepared according to the general procedure from (*E*)-4-benzyloxy-but-2-enal (571 mg, 3.00 mmol), trimethyl-(5-methyl-furan-2-yloxy)-silane (184 μL, 1.00 mmol), (*2S, 5S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (49.2 mg, 0.200 mmol), 2,4-dinitrobenzoic acid (42.4 mg, 0.20 mmol), H_2O (36.0 μL, 2.00 mmol), and CH_2Cl_2 (4.0 mL) at −70 °C for 24 h to provide the title compound as a colorless oil (248.8 mg, 86% yield, >20 : 1 dr, 90% ee) after silica gel chromatography (40% EtOAc/hexanes). IR (film) 3071, 2982, 2939, 2849, 2736, 1758, 1721, 1602, 1452, 1384, 1315, 1273, 1177, 1112, 1071, 1026, 952.4, 822.7, 712.5 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.76 (s, 1H, CHO), 7.93 (d, *J* = 7.1 Hz, 2H, Ar), 7.60-7.38 (m, 4H, Ar, C**H**$CHCO_2$), 6.07 (d, *J* = 6.0 Hz, 1H, $CHC\mathbf{H}CO_2$), 4.41 (dd, *J* = 4.9, 12.1 Hz, 1H, $OC\mathbf{H}_2$), 4.22 (dd, *J* = 5.5, 12.1 Hz, 1H, $OC\mathbf{H}_2$), 3.04- 2.94 (m, 1H, $CH_2C\mathbf{H}CH_2$), 2.72- 2.54 (m, 2H, $C\mathbf{H}_2CHO$), 1.54 (s, 3H, $CC\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.4, 171.7, 166.1, 159.0, 133.7, 129.7, 129.4, 128.8, 121.5, 89.1, 63.9, 41.5, 39.4, 23.8; HRMS (CI) exact mass calcd for ($C_{16}H_{16}O_5$) requires *m/z* 288.0998, found *m/z* 288.1003. $[\alpha]_D$ = + 45.6 (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by HPLC analysis of the alcohol, obtained by $NaBH_4$ reduction of the aldehyde, using a Chiracel AS and AS guard column (10% ethanol / hexanes, 1 mL/min); (*2S, 2'R*) isomer t_r = 47.9 min and (*2R, 2'S*) isomer t_r = 67.0 min.

(*2S, 2'R*)-2-(2'-methyl-5'-oxo-2', 5'-dihydro-furan-2'-yl)-4-oxo-butyric acid methyl ester (Table 2, Entry 6). Prepared according to the general procedure from (*E*)-

methyl-4-oxo-butenoate **9** (228.2 mg, 2.00 mmol), trimethyl-(5-methyl-furan-2-yloxy)-silane (184 μL, 1.00 mmol), *(2S, 5S)*-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (49.2 mg, 0.200 mmol), 2,4-dinitrobenzoic acid (42.4 mg, 0.20 mmol), H_2O (36.0 μL, 2.00 mmol), and trichloroethylene (2.0 mL) at −60 °C for 22 h to provide the title compound as a colorless oil (178.2 mg, 84% yield, 11 : 1 dr, 99% ee) after silica gel chromatography (40% EtOAc/hexanes). IR (film) 3434, 3085, 2954, 2849, 2725, 1760, 1734, 1604, 1437, 1364, 1245, 1172, 1112, 1094, 1045, 956.3, 821.9 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.72 (s, 1H, CHO), 7.58 (d, *J* = 5.5 Hz, 1H, C**H**CHCO$_2$), 6.05 (d, *J* = 5.5 Hz, 1H, CHC**H**CO$_2$), 3.72 (s, 3H, OCH_3), 3.17- 2.79 (m, 3H, C**H**C**H$_2$**CHO), 1.42 (s, 3H, $OCCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.7, 171.3, 170.7, 160.0, 120.7, 87.0, 52.9, 46.8, 41.7, 21.0; HRMS (CI) exact mass calcd for ($C_{10}H_{12}O_5$) requires *m/z* 212.0684, found *m/z* 212.0685. $[\alpha]_D$ = + 50.9 (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by GLC using a Bodman Chiraldex β-DM (30 m x 0.25 mm) column (130 °C isotherm, 1 mL/min); (*2R, 2'S*) isomer t_r = 48.6 min and (*2S, 2'R*) isomer t_r = 50.8 min.

(*3S, 2'R*)-4-Methyl-3-(5-oxo-2,5-dihydro-furan-2-yl)-pentanal (Table 3, Entry 1). Prepared according to the general procedure from (*E*)-4-methyl-2-pentenal (351 μL, 3.00 mmol), 2-(trimethylsilyloxy)furan (168 μL, 1.00 mmol), (*2S, 5S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (49.2 mg, 0.200 mmol), dichloroacetic acid (16.5 μL, 0.20 mmol), H_2O (90.0 μL, 5.00 mmol), and $CHCl_3$ (1.91 mL) at −50 °C for 7 h to provide the title compound as a colorless oil (127.2 mg, 70% yield, 7.3 : 1 dr, 90% ee) after silica gel chromatography (40% EtOAc/hexanes). IR (film) 2963, 2870, 2821, 2731, 1753, 1721, 1599, 1467, 1391, 1372, 1325, 1265, 1250, 1163, 1103, 1024, 985.4, 905.2, 819.6 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.72 (s, 1H, CHO), 7.39 (dd, *J* = 1.4, 5.5 Hz, 1H, C**H**CHCO$_2$), 6.10 (dd, *J* = 1.6, 5.8 Hz, 1H, CHC**H**CO$_2$), 5.22 (m, 1H, OCH), 2.47- 2.23 (m, 2H, CH_2), 1.97- 1.82 (m, 1H, $CHMe_2$), 1.03 (d, *J* = 6.6 Hz, 3H,

$CH(C\mathbf{H_3})_2$); 0.99 (d, *J* = 6.9 Hz, 3H, $CH(C\mathbf{H_3})_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.8, 173.1, 156.8, 122.0, 84.0, 40.7, 40.3, 30.4, 20.7, 20.3; HRMS (CI) exact mass calc'd for ($C_{10}H_{14}O_3$) requires *m/z* 182.0943, found *m/z* 182.0937. $[\alpha]_D$ = – 87.4 (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by GLC using a Bodman Chiraldex B-DM (30 m x 0.25 mm) column (170 °C isotherm, 1 mL/min); (*3R, 2'S*) isomer t_r = 6.7 min and (*3S, 2'R*) isomer t_r = 7.0 min.

(*3R, 2'R*)-3-(2'-Ethyl-5'-oxo-2', 5'-dihydro-furan-2'-yl)-butyraldehyde (Table 3, Entry 3). Prepared according to the general procedure from (*E*)-crotonaldehyde (248 μL, 3.00 mmol), trimethyl-(5-ethyl-furan-2-yloxy)-silane (184 mg, 1.00 mmol), (*2S, 5S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (49.2 mg, 0.200 mmol), 2,4-dinitrobenzoic acid (42.4 mg, 0.20 mmol), H_2O (36.0 μL, 2.00 mmol), and CH_2Cl_2 (6.0 mL) at –70 °C for 11 h to provide the title compound as a colorless oil (155.7 mg, 83% yield, 16 : 1 dr, 90% ee) after silica gel chromatography (40% EtOAc/hexanes). IR (film) 3093, 2978, 2929, 2874, 2722, 1759, 1724, 1602, 1460, 1384, 1218, 1124, 975.9, 918.7, 822.2 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.57 (t, *J* = 1.6 Hz, 1H, CHO), 7.26 (d, *J* = 5.5 Hz, 1H, $C\mathbf{H}CHCO_2$), 6.00 (d, *J* = 5.5 Hz, 1H, $CHC\mathbf{H}CO_2$), 2.58- 2.46 (m, 1H, $C\mathbf{H}CH_3$), 2.38 (dd, *J* = 3.8, 17.6 Hz, 1H, $C\mathbf{H}_2CHO$), 2.07 (ddd, *J* = 1.6, 8.8, 17.0 Hz, 1H, $C\mathbf{H}_2CHO$), 1.90- 1.60 (m, 2H, $C\mathbf{H_2}CH_3$), 0.85 (d, *J* = 6.6 Hz, 3H, $CHC\mathbf{H_3}$), 0.68 (t, *J* = 7.1 Hz, 3H, $CH_2C\mathbf{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.8, 172.4, 157.7, 122.6, 93.4, 45.6, 33.5, 28.2, 16.0, 7.7; HRMS (CI) exact mass calc'd for ($C_{10}H_{14}O_3$) requires *m/z* 182.0943, found *m/z* 182.0942. $[\alpha]_D$ = + 25.5 (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by GLC using a Bodman Chiraldex Γ-TA (30 m x 0.25 mm) column (150 °C isotherm, 1 mL/min); (*3S, 2'S*) isomer t_r = 27.0 min and (*3R, 2'R*) isomer t_r = 29.8 min.

(*2S,1'R*)-2-(1'-methyl-3'-oxo-propyl)-5-oxo-2,5-dihydrofuran-2-carboxylic acid methyl ester (Table 3, Entry 4). Prepared according to the general procedure from (*E*)-crotonaldehyde (81.0 μL, 0.981 mmol), 5-triisopropylsilanyloxy-furan-2-carboxylic acid methyl ester **6** (97.5 mg, 0.327 mmol), the trifluoroacetic acid salt of (*2S, 5S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (23.6 mg, 0.065 mmol), H_2O (12.0 μL, 0.654 mmol), and THF (3.3 mL) at −10 °C for 44 h to provide the title compound as a colorless oil (60.0 mg, 86% yield, 6 : 1 dr, 98% ee) after silica gel. IR (film): 3099, 2960, 2737, 1774, 1738, 1260, 1118, 1040, 908.8, 822.6 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.71 (d, *J* = 0.9 Hz, 1H, CHO), 7.40 (d, *J* = 5.4 Hz, 1H, CH=C**H**), 6.19 (d, *J* = 5.4 Hz, 1H, C**H**=CH), 3.77 (s, 1H, $CO_2C\mathbf{H}_3$), 3.05 (ddq, *J* = 6.6, 3.9, 3.9 Hz, 1H, C**H**CH_2), 2.63 (dd, *J* = 18.0, 3.9 Hz, 1H, CHC**H**HCHO),), 2.49 (ddd, *J* = 18.0, 3.9, 1.2 Hz, 1H, CHCH**H**CHO), 0.83 (t, *J* = 6.6 Hz, 3H, CHC$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.2, 171.0, 167.6, 153.6, 122.6, 91.9, 53.4, 45.9, 32.4, 13.9; HRMS (CI) exact mass calc'd for ($C_{10}H_{13}O_5$) requires *m/z* 213.0763, found *m/z* 213.0763. $[\alpha]_D$ = −59.1 (c = 1.4, $CHCl_3$). The diastereomeric ratio was determined by ^1H NMR. The enantiomeric ratio was determined by GLC analysis of the aldehyde using a Bodman Chiraldex Γ-TA (30 m x 0.25 mm) column (165 ˚C isotherm, 0.8 mL/min); *(2S,1'R)* isomer t_r = 16.8 min, *(2R,1'S)* isomer t_r = 19.2 min.

(*2R,1'R*)-2-(1'-methyl-3'-oxo-propyl)-5-oxo-2,5-dihydrofuran-2-carboxylic acid methyl ester (Table 3, Entry 5). Prepared according to the general procedure from (*E*)-crotonaldehyde (81.0 μL, 0.98 mmol), 5-triisopropylsilanyloxy-furan-2-carboxylic acid methyl ester **6** (97.2 mg, 0.33 mmol), the trifluoromethanesulfonic acid salt of *(2S, 5S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (25.8 mg, 0.065 mmol), H_2O (11.7 μL, 0.65 mmol), and $CHCl_3$ (3.3 mL, 0.1 M) at −10 °C for 4 d to provide the title compound as a colorless oil (60.2 mg, 83% yield, 7 : 1 dr, 98% ee) after silica gel. IR

(film): 3099, 2960, 2734, 1773, 1738, 1254, 1117, 1038, 908.2, 821.5 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.67 (s, 1H, C**H**O), 7.38 (d, *J* = 5.4 Hz, 1H, CH=C**H**), 6.14 (d, *J* = 5.4 Hz, 1H, C**H**=CH), 3.79 (s, 1H, $CO_2C\mathbf{H_3}$), 3.04 (ddq, *J* = 7.2, 6.6, 5.7 Hz, 1H, C**H**CH_2), 2.45 (dd, *J* = 18.6, 5.4 Hz, 1H, C**H**HCHO), 2.32 (ddd, *J* = 18.0, 7.2, 0.9 Hz, 1H, CH**H**CHO), 0.83 (t, *J* = 6.6 Hz, 3H, CHC$\mathbf{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.4, 170.8, 167.3, 154.2, 122.3, 92.1, 53.4, 44.3, 32.5, 15.9; HRMS (EI) exact mass calc'd for ($C_{10}H_{12}O_5$) requires *m/z* 212.0684, found *m/z* 212.0682. $[\alpha]_D = -79.5$ (c = 1.4, $CHCl_3$). The diastereomeric ratio was determined by ^1H NMR. The enantiomeric ratio was determined by GLC analysis of the aldehyde using a Bodman Chiraldex Γ-TA (30 m x 0.25 mm) column (165 ˚C isotherm, 0.8 mL/min); *(2R,1'R)* isomer t_r = 17.9 min, *(2S,1'S)* isomer t_r = 19.7 min.

(*3R, 2'R*)-3-(2',4'-Dimethyl-5'-oxo-2', 5'-dihydro-furan-2'-yl)-butyraldehyde (Table 3, Entry 6). Prepared according to the general procedure from (*E*)-crotonaldehyde (124 μL, 1.50 mmol), trimethyl-(3,5-dimethyl-furan-2-yloxy)-silane (102 mg, 0.500 mmol), (*2S*, *5S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (24.6 mg, 0.100 mmol), 2,4-dinitrobenzoic acid (21.2 mg, 0.20 mmol), H_2O (18.0 μL, 1.00 mmol), and CH_2Cl_2 (2.0 mL) at −65 °C for 23 h to provide the title compound as a colorless oil (66.5 mg, 73% yield, 24 : 1 dr, 90% ee) after silica gel chromatography (40% EtOAc/hexanes). IR (film) 2980, 2929, 2885, 2831, 2732, 1754, 1723, 1662, 1449, 1378, 1324, 1258, 1138, 1089, 1069, 1051, 999.8, 941.6, 876.1, 761.5 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.67 (dd, *J* = 1.1, 2.2 Hz, 1H, CHO), 6.95 (q, *J* = 1.6 Hz, 1H, C**H**CCH_3CO_2), 2.54- 2.40 (m, 2H, C**H**C$\mathbf{H_2}$CHO), 2.15 (ddd, *J* = 2.2, 9.3, 17.6 Hz, 4H, C$\mathbf{H_2}$C$\mathbf{H_2}$), 1.86 (d, *J* = 1.6 Hz, 3H, C$\mathbf{H_3}CCO_2$), 1.39 (s, 3H, $OCCH_3$), 0.94 (d, *J* = 7.1 Hz, 3H, CHC$\mathbf{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.8, 173.3, 151.2, 130.3, 88.2, 46.0, 35.3,

23.2, 16.2, 11.0; HRMS (CI) exact mass calcd for ($C_{10}H_{14}O_3$) requires *m/z* 182.0943, found *m/z* 182.0933. $[\alpha]_D$ = +22.3 (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by GLC using a Bodman Chiraldex Γ-TA (30 m x 0.25 mm) column (130 °C isotherm, 1 mL/min); (*3R, 2'R*) isomer t_r = 48.9 min and (*3S, 2'S*) isomer t_r = 61.9 min.

(*2R,1'S*)-2-(1'-*tert*-butoxycarbonyl-3'-oxo-propyl)-5-oxo-2,5-dihydrofuran-2-carboxylic acid methyl ester (8). To a stirring solution of the (2*R*, 5*R*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one • TFA salt (72.3 mg, 0.200 mmol) and H_2O (36 μL, 2.00 mmol) in THF (8 mL) was added 4-oxobut-2-enoic acid *tert*-butyl ester **7** (469 mg, 3.00 mmol) at room temperature. The resulting solution was cooled to 4 ˚C before 5-Triisopropylsilanyloxy-furan-2-carboxylic acid methyl ester **6** (300 mg, 1.01 mmol) was added in 2 mL of THF. The solution was stirred at 4 ˚C for 43 h then passed through a pad of silica gel and concentrated. After silica gel chromatography, aldehyde **8** was isolated as a yellow solid after reconcentration from hexanes (268 mg, 90% yield, 11:1 d.r., 89% e.e.). IR (film): 2918, 2852, 1775, 1733, 1720, 1458, 1366, 1239, 1145, 1108, 1021, 828.8 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.69 (s, 1H, C**H**O), 7.60 (d, *J* = 5.7 Hz, 1H, CH=C**H**), 6.17 (d, *J* = 6.3 Hz, 1H, C**H**=CH), 3.81 (dd, *J* = 9.9, 4.5 Hz, 1H, C**H**$CO_2C(CH_3)_3$), 3.79 (s, 3H, $CO_2C\mathbf{H_3}$), 2.92 (dd, *J* = 18.0, 9.3 Hz, 1H, CH**H**-CHO), 2.58 (dd, *J* = 18.6, 3.9 Hz, 1H, C**H**H-CHO), 1.39 (s, 9H, $C(C\mathbf{H_3})_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.0, 170.5, 168.0, 166.8, 153.9, 122.3, 88.6, 83.4, 54.0, 45.0, 40.8, 28.0 (3); HRMS (CI) exact mass calc'd for ($C_{14}H_{19}O_7$) requires *m/z* 299.1131, found *m/z* 299.1121. $[\alpha]_D$ = +9.9 (c = 0.95, $CHCl_3$). The diastereomeric ratio was determined by GLC analysis of the aldehyde using a Bodman Chiraldex Γ-TA (30 m x 0.25 mm) column (170 ˚C, 1.0 mL/min); *(2R,1'S)/(2S,1'R)* isomers t_r= 28.2 min, *(2S,1'S)/(2R,1'R)* isomers t_r = 30.3 min. The enantiomeric ratio was determined by HPLC analysis of the 2,2-dimethylpropane acetal, obtained by acetal formation on the aldehyde with 2,2-dimethylpropane-1,3-diol

and paratoluenesulfonic acid, using a Chiralcel OD-H and OD-H guard column (1.5% EtOH/hexanes, 214 nm, 1.0 mL/min); *(2S,1'R)* isomer t_r = 19.6 min, *(2R,1'S)* isomer t_r = 16.6 min.

(*2R,1'S*)-2-(1'-*tert*-butoxycarbonyl-undec-3'-enyl)-5-oxo-2,5-dihydrofuran-2-carboxylic acid methyl ester. Chromous chloride (383 mg, 3.12 mmol) and *N*,*N*-dimethyl formamide (243 μL, 3.12 mmol) were stirred in anhydrous THF (7.8 mL) under an N_2 atmosphere at room temperature for 1 h to generate the $CrCl_2$:DMF complex[5]. 1,1-diiodooctane[6] (287 mg, 0.780 mmol) and aldehyde **8** (100 mg, 0.390 mmol) were added in 1.3 mL of anhydrous THF . TLC analysis showed consumption of the aldehyde after 3.5 h. The reaction was quenched with H_2O and the aqueous layer was extracted three times with pentanes. The pentane layers were dried (Na_2SO_4) and concentrated. The title compound was afforded as a white solid after silica gel chromatography (77 mg, 65% yield). IR (film): 2956, 2928, 2856, 1783, 1740, 1723, 1457, 1437, 1369, 1256, 1156, 1099 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, *J* = 5.4 Hz, 1H, C**H**=CH), 6.18 (d, *J* = 5.4 Hz, 1H, CH=C**H**), 5.46 (dt, *J* = 15.3, 6.6 Hz, 1H, CH_2C**H**=$CHCH_2$), 5.25 (dt, *J* = 15.6, 6.6 Hz, 1H, CH_2CH=C**H**CH_2), 3.77 (s, 3H, CO_2C**H**$_3$), 3.21 (dd, *J* = 9.6, 4.8 Hz, 1H, C**H**$CO_2C(CH_3)_3$), 2.20 (m, 2H, CHC**H**$_2$CH=CH), 1.94 (dt, *J* =6.6, 6.0 Hz, 2H, CH=CHC**H**$_2$), 1.41 (s, 9H, $CO_2C(C$**H**$_3)_3$), 1.24 (m, 10H, (C**H**$_2)_5$), 0.87 (t, *J* = 6.6 Hz, 3H, CH_2C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 169.7, 167.2, 153.7, 134.5, 124.9, 122.7, 89.4, 82.3, 53.7, 51.2, 32.8, 32.1, 30.7, 29.5, 29.4, 28.2 (3), 23.0, 14.4; HRMS (CI) exact mass calc'd for $(C_{22}H_{35}O_6)^+$ requires *m/z* 395.2433, found *m/z* 395.2428. $[\alpha]_D$ = -3.9 (c = 0.98, $CHCl_3$).

(*2R,1'S*)-2-(1'-*tert*-butoxycarbonyl-undecyl)-5-oxo-tetrahydrofuran-2-carboxylic acid methyl ester. A 25 mL round bottom flask equipped with a magnetic

stir bar and containing the undecenyl *tert*-butyl ester (100 mg, 0.284 mmol) and activated palladium on carbon (10 mg) was charged with degassed EtOAc (2.8 mL, 0.1M). The system was evacuated and purged with H_2 gas three times. TLC analysis showed the reaction complete after 4.5 h, at which point the reaction mixture was filtered over a pad of Celite and a pad of silica gel with EtOAc to afford the title compound as a clear oil after concentration (94.0 mg, 92% yield). IR (film): 2957, 2927, 2855, 1797, 1744, 1731, 1460, 1369, 1249, 1169, 1132, 1055 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.78 (s, 3H, $CO_2C\mathbf{H_3}$), 2.94 (dd, *J* = 10.8, 3.0 Hz, 1H, $C\mathbf{H}CO_2C(CH_3)_3$), 2.50 (m, 4H, $C\mathbf{H_2}C\mathbf{H_2}CO_2C$), 1.73 (m, 1H, $CHC\mathbf{H}H(CH_2)_8$), 1.47 (m, 1H, $CHCH\mathbf{H}(CH_2)_8$), 1.43 (s, 9H, $CO_2C(C\mathbf{H_3})_3$), 1.23 (m, 16H, $(C\mathbf{H_2})_8$), 0.85 (t, *J* = 6.6 Hz, 3H, $CH_2C\mathbf{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5, 171.1, 170.8, 86.7, 81.9, 53.2, 51.9, 32.1, 29.8, 29.8, 29.6, 29.6, 29.5, 28.4, 28.3, 28.2 (3), 22.9, 14.4; HRMS (CI) exact mass calc'd for $(C_{22}H_{39}O_6)^+$ requires *m/z* 399.2746, found *m/z* 399.2736. $[\alpha]_D$ = -21.4 (c = 1.1, $CHCl_3$).

(-)-Spiculisporic acid (5). (*2S,1'R*)-2-(1'-*tert*-butoxycarbonyl-undecyl)-5-oxo-tetrahydrofuran-2-carboxylic acid methyl ester (28.7 mg, 0.0805 mmol) was taken up in 0.5 mL THF and 1 mL of 4N aqueous NaOH. The biphasic mixture was refluxed at 100 ˚C for 5.5 h and then cooled to room temperature. The reaction mixture was acidified with 1N aqueous HCl to pH=1. The aqueous layer was extracted four times with EtOAc. The organic layers were concentrated to a white solid. The hydrolyzed intermediate was dissolved in a small amount of THF and 2 mL of 1N aqueous HCl was added. The reaction mixture was refluxed at 100 ˚C for 3.5 h, after which it was cooled to room temperature and extracted four times with EtOAc. The organic layers were dried (Na_2SO_4) and concentrated. The product was recrystallized from hot water to yield the title compound **5** as white crystals (20 mg, 76% yield). IR (film): 2919, 2850, 1793, 1778, 1716, 1654, 1559, 1540, 1510, 1458, 1419, 1290, 1182, 927.3 cm^{-1}; ^1H NMR (300

MHz, CD_3OD) δ 3.01 (dd, *J* = 10.8, 2.7 Hz, 11H, C**H**CO_2H), 2.53 (m, 4H, C**H**$_2$C**H**$_2$$CO_2$C), 1.85 (m, 1H, CHC**H**H$(CH_2)_8$), 1.52 (m, 1H, CHCH**H**$(CH_2)_8$), 1.29 (m, 16H, (C**H**$_2$)$_8$), 0.90 (t, *J* = 6.6 Hz, 3H, CH_2C**H**$_3$); ^{13}C NMR (75 MHz, CD_3OD $_3$) δ 178.3, 175.3, 173.9, 88.1, 52.5, 33.3, 30.9, 30.8, 30.8, 30.7, 30.6, 30.5, 29.2, 29.0, 29.0, 23.9, 14.7; HRMS (FAB+) exact mass calc'd for $(C_{17}H_{29}O_6)^+$ requires *m/z* 329.1964, found *m/z* 329.1965. $[\alpha]_D$ = -10.9 (c = 0.427, EtOH). Commercial (-)-spiculisporic acid: $[\alpha]_D$ = -10.2 (c = 1.0, EtOH). ^{1}H, ^{13}C, and IR spectra of synthetic **5** were identical to the commercial spiculisporic acid.

(*2S,1'S*)-2-(1'-Methoxycarbonyl-3'-oxo-propyl)-5-oxo-2,5-dihydrofuran-2-carboxylic acid methyl ester (10). 4-Oxobut-2-enoic acid methyl ester **9** (574 mg, 5.03 mmol) was added to a stirring solution of (2*R*, 5*R*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (82.6 mg, 0.335 mmol), trifluoromethanesulfonic acid (30 μL, 0.335 mmol), and H_2O (60 μL, 3.35 mmol) in $CHCl_3$ (16.8 mL, 0.1 M) at room temperature. The reaction mixture was cooled to -20 ˚C. 5-Triisopropylsilanyloxy-furan-2-carboxylic acid methyl ester **6** (500 mg, 1.68 mmol) was added at -20 ˚C in 1 mL $CHCl_3$. The reaction mixture was stirred for 40 h, filtered over a silica plug, and concentrated. After silica gel chromatography, aldehyde **10** was isolated as a pale yellow solid after reconcentration from hexanes (278 mg, 65% yield, 22:1 d.r., 97% e.e.). IR (film): 3103, 2956, 2849, 1783, 1739, 1603, 1437, 1247, 1189, 1086, 1031, 917.8, 820.2 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.72 (s, 1H, C**H**O), 7.48 (d, *J* = 5.4 Hz, 1H, CH=C**H**), 6.20 (d, *J* = 5.4 Hz, 1H, C**H**=CH), 3.94 (dd, *J* = 7.2, 4.8 Hz, 1H, C**H**CO_2CH_3), 3.80 (s, 3H, CO_2C**H**$_3$), 3.73 (s, 3H, CO_2C**H**$_3$), 3.11 (dd, *J* = 19.2, 7.5 Hz, 1H, CH**H**-CHO), 2.55 (dd, *J* = 18.6, 4.8 Hz, 1H, C**H**H-CHO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.1, 170.5, 169.4, 166.9, 153.8, 122.9, 88.9, 53.8, 53.3, 43.5, 39.9; HRMS (EI+) exact mass calc'd for ($C_{11}H_{12}O_7$) requires *m/z* 256.0583, found *m/z* 256.0576. $[\alpha]_D$ = -124.0 (c = 0.97, $CHCl_3$).

The enantiomeric ratio was determined by GLC analysis of the aldehyde using a Bodman Chiraldex Γ-TA (30 m x 0.25 mm) column (155 ˚C, 1.0 mL/min); *(2R,1'R)* isomer t_r = 62.8 min, *(2S,1'S)* isomer t_r = 58.4 min.

(*2S,1'S*)-2-(1'-Methoxycarbonyl-undec-3'-enyl)-5-oxo-2,5-dihydrofuran-2-carboxylic acid methyl ester. Chromous chloride (383 mg, 3.12 mmol) and *N*,*N*-dimethyl formamide (243 μL, 3.12 mmol) were stirred in anhydrous THF (7.8 mL) under an N_2 atmosphere at room temperature for 1 h to generate the $CrCl_2$:DMF complex.[5] 1,1-diiodooctane[6] (287 mg, 0.780 mmol) and aldehyde **10** (100 mg, 0.390 mmol) were added in 1.3 mL of anhydrous THF . TLC analysis showed consumption of the aldehyde after 3.5 h. The reaction was quenched with H_2O and the aqueous layer was extracted three times with pentanes. The pentane layers were dried (Na_2SO_4) and concentrated. The title compound was afforded as a white solid after silica gel chromatography (77 mg, 65% yield). IR (film): 2956, 2922, 2852, 1777, 1742, 1724, 1439, 1260, 1186, 1101, 968.8, 916.5, 833.0 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, *J* = 5.4 Hz, 1H, C**H**=CH), 6.00 (d, *J* = 5.4 Hz, 1H, CH=C**H**), 5.22 (dt, *J* = 15.3, 6.6 Hz, 1H, CH_2C**H**=CHCH_2), 5.09 (dt, *J* = 15.3, 6.6 Hz, 1H, CH_2CH=C**H**CH_2), 3.58 (s, 3H, CO_2C**H$_3$**), 3.50 (s, 3H, CO_2C**H$_3$**), 3.12 (dd, *J* = 8.1, 4.8 Hz, 1H, C**H**CO_2CH_3), 2.18 (m, 1H, C**H**HCH=CH), 2.03 (m, 1H, CH**H**CH=CH), 1.73 (dt, *J* = 6.9, 6.0 Hz, 2H, CH=CHC**H$_2$**), 1.03 (m, 10H, (C**H$_2$**)$_5$), 0.66 (t, 3H, *J* = 6.6 Hz, CH_2C**H$_3$**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 170.2, 167.4, 153.3, 134.5, 125.3, 122.8, 89.6, 53.7, 52.5, 50.1, 32.7, 32.0, 29.5, 29.4, 29.3, 29.3, 22.9, 14.3; HRMS (EI) exact mass calc'd for ($C_{19}H_{28}O_6$) requires *m/z* 352.1886, found *m/z* 352.1881. $[\alpha]_D$ = -70.0 (c = 1.0, $CHCl_3$).

(*2S,1'S*)-2-(1'-Methoxycarbonyl-undecyl)-5-oxo-tetrahydrofuran-2-carboxylic acid methyl ester. A 25 mL round bottom flask equipped with a magnetic

stir bar and containing (*2R,1'R*)-2-(1'-Methoxycarbonyl-undec-3'-enyl)-5-oxo-2,5-dihydrofuran-2-carboxylic acid methyl ester (100 mg, 0.284 mmol) and activated palladium on carbon (10 mg) was charged with degassed EtOAc (2.8 mL, 0.1M). The system was evacuated and purged with H_2 gas three times. The reaction was stirred at ambient temperature under a hydrogen atmosphere until TLC analysis showed the reaction complete after 4.5 h, at which point the reaction mixture was filtered over a pad of Celite and a pad of silica gel with EtOAc to afford the title compound as a clear oil after concentration (101 mg, quantatative yield). IR (film): 2955, 2926, 2855, 1796, 1740, 1456, 1436, 1269, 1230, 1165, 1060, 985.5, 896.9 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.79 (s, 3H, $CO_2C\mathbf{H_3}$), 3.70 (s, 3H, $CO_2C\mathbf{H_3}$), 3.11 (dd, *J* = 10.8, 3.3 Hz, 1H, $C\mathbf{H}CO_2CH_3$), 2.60 (m, 4H, $C\mathbf{H_2}C\mathbf{H_2}CO_2$), 1.77 (m, 1H, $CHC\mathbf{H}H(CH_2)_8$), 1.56 (m, 1H, $CHCH\mathbf{H}(CH_2)_8$), 1.25 (m, 16H, $(C\mathbf{H_2})_\mathbf{8}$), 0.87 (t, 3H, *J* = 6.6 Hz, $CH_2C\mathbf{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.3, 172.2, 170.6, 86.5, 60.7, 53.5, 52.3, 50.4, 32.1, 29.8, 29.8, 29.6, 29.6, 28.2, 28.1, 27.5, 27.3, 23.0, 14.4; HRMS (CI) exact mass calc'd for $(C_{19}H_{33}O_6)^+$ requires *m/z* 357.2277, found *m/z* 357.2273. $[\alpha]_D$ = +10.3 (c = 1.0, $CHCl_3$).

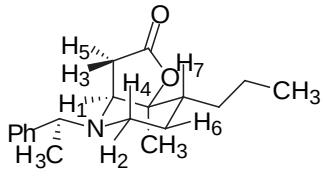
(-)-5-Epi-spiculisporic acid (11). (*2R,1'R*)-2-(1'-Methoxycarbonyl-undecyl)-5-oxo-tetrahydrofuran-2-carboxylic acid methyl ester (28.7 mg, 0.0805 mmol) was taken up in 0.5 mL THF and 1 mL of 4N aqueous NaOH. The biphasic mixture was refluxed at 100 ˚C for 5.5 h and then cooled to room temperature. The reaction mixture was acidified with 1N aqueous HCl to pH=1. The aqueous layer was extracted four times with EtOAc. The organic layers were concentrated to a white solid. The hydrolyzed intermediate was dissolved in a small amount of THF and 2 mL of 1N aqueous HCl was added. The reaction mixture was refluxed at 100 ˚C for 3.5 h, after which it was cooled to room temperature and extracted four times with EtOAc. The organic layers were dried (Na_2SO_4) and concentrated to a white solid which was then recrystallized from hot water

to yield (+)-5-epi-spiculisporic acid **11** as a white solid (20 mg, 76% yield). IR (film): 2917, 2850, 1801, 1709, 1466, 1420, 1182, 1133, 1055, 953.8 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 3.03 (dd, *J* = 9.3, 4.2 Hz, 1H, C**H**CO_2H), 2.57 (m, 4H, C$\mathbf{H_2}$C$\mathbf{H_2}$$CO_2$C), 1.66 (m, 2H, CHC$\mathbf{H_2}$$(CH_2)_8$), 1.30 (m, 16H, (C$\mathbf{H_2}$)$_\mathbf{8}$), 0.90 (t, *J* = 6.6 Hz, 3H, CH_2C$\mathbf{H_3}$); ^{13}C NMR (75 MHz, CD_3OD) δ 178.4, 175.4, 173.8, 88.0, 51.9, 33.3, 30.9, 30.9, 30.7, 30.7, 30.7, 29.5, 29.1, 29.0, 28.3, 24.0, 14.7; HRMS (FAB+) exact mass calc'd for $(C_{17}H_{29}O_6)^+$ requires *m/z* 329.1964, found *m/z* 329.1962. $[\alpha]_D$ = -6.3 (c = 0.75, EtOH).

General procedure for reductive amination and heteroconjugate addition to form 2,3,3',4-tetrasubstituted piperidine adducts. The γ-butenolide (1.0 equiv) was taken up in THF (0.25 M). (*L*)-α-Methylbenzylamine (2.0 equiv) was added to the solution, followed by sodium triacetoxyborohydride (STAB, 1.5 equiv). The reaction was stirred vigorously at ambient temperature until TLC analysis showed consumption of the aldehyde. The reaction was quenched with a saturated aqueous solution of Rochelle's salt and stirred for 12-15 h at ambient temperature. The aqueous phase was extracted three times with EtOAc. The organic layers were dried (Na_2SO_4) and concentrated. The 2,3,3',4-tetrasubstituted piperidine product was isolated after silica gel chromatography (100% CH_2Cl_2).

(*7aS,7R*)-7a-Methyl-4-((*1S*)-1-phenylethyl)-7-propylhexahydro-furo[3,2-*b*]pyridin-2-one. Prepared according to the general procedure above using the methyl γ-butenolide of 2-hexenal (Table 2, entry 2) (500 mg, 2.55 mmol), (*L*)-α-methylbenzylamine (400 μL, 5.10 mmol), STAB (810 mg, 3.83 mmol), and THF (10.2 mL). The title compound was isolated as a yellow oil (573 mg) in 75% yield. IR (film): 2957, 2934, 2872, 2806, 1772, 1653, 1457, 1230, 1086, 943.4 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 5H, Ar**H**), 3.44 (q, *J* = 6.6 Hz, 1H, N**H**CHAr), 3.25 (dd, *J* = 12.3, 7.8

Hz, NHC**H**CH_2), 3.03 (dt, *J* = 12.0, 3.3 Hz, 1H, NHC**H**HCH_2), 2.72 (dd, *J* = 17.1, 12.6 Hz, 1H, CHC**H**HCO), 2.34 (dt, *J* =12.3, 3.0 Hz, 1H, NHCH**H**CH_2), 2.08 (dd, *J* = 16.5, 7.2 Hz, 1H, CHCH**H**CO), 1.76 (dq, *J* = 13.2, 3.3 Hz, 1H, CH_2C**H**HCH), 1.57 (m, 1H, C**H**$CH_2CH_2CH_3$), 1.40 (m, 2H, CH_2CH**H**CH and C**H**HCH_2CH_3), 1.33 (d, *J* = 6.3 Hz, 3H, NHCHC**H$_3$**), 1.32 (s, 3H, CC**H$_3$**), 1.16 (m, 3H, CH**H**C**H$_2$**CH_3), 0.85 (t, *J* = 7.2 Hz, 3H, CH_2C**H$_3$**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.2, 144.1, 128.5 (2), 127.2, 126.7 (2), 85.9, 63.4, 62.1, 42.2, 41.5, 31.9, 28.3, 25.5, 21.4,20.7, 18.8, 14.4; HRMS (EI) exact mass calc'd for ($C_{19}H_{27}NO_2$) requires *m/z* 301.2043, found *m/z* 301.2042. $[\alpha]_D$ = −106.5 (c = 1.0, $CHCl_3$).



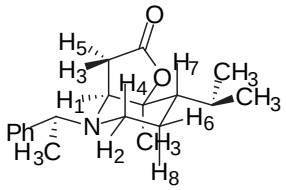
The stereochemistry was confirmed by the presence of an nOe between H_3 and H_4 (7.3%), H_4 and H_7 (5.7%) and H_3 and H_7 (5.7%). Furthermore, there were nOe interactions between H_5 and H_1 (5.1%), H_1 and the methyl group at the 3-piperidine position (7.4%), and H_5 and the methyl group at the 3-piperidine position (5.8%).

(*7aS,7S*)-7a-Methyl-7-phenyl-4-((*1S*)-1-phenylethyl)-hexahydro-furo[3,2-*b*]pyridin-2-one. Prepared according to the general procedure above using the methyl γ-butenolide cinnamaldehyde (Table 2, Entry 4) (470 mg, 2.04 mmol), (*L*)-α-methylbenzylamine (325 μL, 4.08 mmol), STAB (650 mg, 3.06 mmol), and THF (8.2 mL). The *uncyclized* title compound was isolated as a yellow oil (406 mg) in 60% yield, which cyclized to the title compound upon standing at room temperature for several days. The product was isolated as colorless crystals. IR (film): 3060, 3028, 2976, 2941, 2878, 2852, 1770, 1493, 1452, 1217, 1154, 933.2, 727.6, 700.3 cm^{-1}; ^{1}H NMR (300 MHz,

$CDCl_3$) δ 7.36 (m, 10H, Ar**H**), 3.94 (q, *J* = 6.6 Hz, 1H, N**H**CHAr), 3.47 (d, *J* = 4.8 Hz, NHC**H**CH_2), 2.87 (dd, *J* = 17.7, 5.1 Hz, 1H, NHC**H**HCH_2), 2.73 (dd, *J* = 13.2, 4.5 Hz, 2H), 2.52 (m, 2H), 2.06 (m, 1H), 1.65 (dq, *J* = 13.2, 3.9 Hz, 1H), 1.41 (d, *J* = 6.6 Hz, 3H, NHCHC**H**$_3$), 1.26 (s, 3H, CC**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.0, 143.0, 140.1, 129.4 (2), 128.0 (2), 127.9 (2), 127.0 (2), 126.7, 126.6, 85.6, 61.4, 56.2, 49.6, 42.7, 35.6, 27.6, 25.1, 11.9; HRMS (EI) exact mass calc'd for ($C_{22}H_{25}NO_2$) requires *m/z* 335.1885, found *m/z* 335.1890. $[\alpha]_D$ = −67.4 (c = 2.3, $CHCl_3$). The stereochemistry of the title compound was confirmed by single crystal X-ray diffraction of the title compound (*vide infra*).

(*7aS,7R*)-7a-Methyl-7-*iso*-propyl-4-((*1S*)-1-phenylethyl)hexahydro-furo[3,2-*b*]pyridin-2-one. Prepared according to the general procedure above using the methyl γ-butenolide of 4-methyl-2-pentenal (Table 2, Entry 3) (620 mg, 3.16 mmol), (*L*)-α-methylbenzylamine (500 μL, 6.32 mmol), STAB (1.00 g, 4.74 mmol), and THF (12.6 mL). The title compound was isolated as a yellow oil (503 mg) in 54% yield. IR (film): 2960, 2875, 2805, 1770, 1454, 1381, 1232, 1080, 943.4, 765.9, 702.2 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (m, 5H, Ar**H**), 3.58 (dd, *J* = 12.3, 7.2 Hz, 1H, NHC**H**CH_2), 3.49 (q, *J* = 6.6 Hz, NC**H**Ar), 2.76 (dd, *J* = 16.5, 12.0 Hz, 1H, CHC**H**HCO), 2.62 (dt, *J* = 12.3, 3.3 Hz, 1H, NHC**H**HCH_2), 2.22 (dt, *J* =12.0, 2.7 Hz, 1H, NHCH**H**CH_2), 2.15 (dd, *J* = 17.1, 7.8 Hz, 1H CHCH**H**CO), 1.76 (sept, *J* = 6.6 Hz, 1H, C**H**(CH_3)$_2$), 1.59 (dq, *J* = 12.3, 3.0 Hz, 1H, CH_2C**H**HCH), 1.52 (s, 3H, CC**H**$_3$), 1.31 (d, *J* = 6.6 Hz, 3H, NHC**H**Ar), 1.18 (2H, m, CH_2C**H***i*-Pr and CH_2CH**H**CH), 1.00 (d, *J* = 7.2 Hz, 3H, CH(C**H**$_3$) (CH_3)), 0.87 (d, *J* = 6.6 Hz, 3H, CH(CH_3) (C**H**$_3$)); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9, 144.6, 128.2 (2), 126.9, 127.7 (2), 86.6, 63.2, 62.2, 47.5, 44.1, 27.7, 25.7, 25.5, 23.1, 20.7, 20.5, 20.0;

HRMS (EI) exact mass calc'd for ($C_{19}H_{27}NO_2$) requires *m/z* 301.2042, found *m/z* 301.2045. $[\alpha]_D = -106.5$ (c = 1.0, $CHCl_3$).



The stereochemistry was confirmed by the presence of an nOe between H_3 and H_4 (13.2%), H_4 and H_7 (5.1%) and H_3 and H_7 (7.6%). Furthermore, there were nOe interactions between H_5 and H_1 (5.5%), H_1 and the methyl group at the 3-piperidine position (6.6%), H_8 and the methyl group at the 3-piperidine position (3.2%), and H_1 and H_8 (2.2%)

(*5S,1'R*)-5-Methyl-5-[1'-methyl-3'-((*1S*)-1-phenylethylamino)-propyl]-5*H*-furan-2-one hydrochloride. The methyl γ-butenolide of crotonaldehyde (Table 2, Entry 1) (206 mg, 1.23 mmol) was taken up in THF (4.9 mL, 0.25 M). (*L*)-α-Methylbenzylamine (195 μL, 2.45 mmol) was added to the solution, followed by addition of STAB (389 mg, 3.81.843 mmol). The reaction was stirred at ambient temperature for 15 min, after which saturated aqueous $NaHCO_3$ was added and stirred for an additional hour. The aqueous mixture was extracted with EtOAc three times, dried ($MgSO_4$) and concentrated. The *uncyclized* reductive amination product was isolated after silica gel chromatography (1% Et_3N/99% CH_2Cl_2 then 2% Et_3N/3% MeOH/95% CH_2Cl_2 flush) as a yellow oil (199 mg) in 60% yield. The hydrochloric acid salt of the reductive amination product was prepared by taking up the amine (61.4 mg, 0.225 mmol) in Et_2O and adding 113 μL of a 2M solution of HCl in Et_2O. The HCl salt precipitated out and the solid was filtered and washed with Et_2O to afford the title compound as a white powder (67.4 mg,

quantative yield). IR (film): 2976, 2734, 2464, 1752, 1588, 1456, 1382, 1241, 1120, 952.2, 822.4, 766.6 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 10.28 (bs, 1H, N**H**H), 9.95 (bs, 1H, NH**H**), 7.64 (m, 2H, C**H**=CH and Ar**H**), 7.44 (m, 4H, Ar**H**), 6.00 (d, *J* = 5.4 Hz, CH=C**H**), 4.24 (m, 1H, NHC**H**Ar), 2.82 (m, 1H), 2.63 (m, 1H), 2.12 (m, 1H), 1.85 (d, *J* = 6.6 Hz, 3H, NHCHC**H**$_3$), 1.82 (m, 1H), 1.40 (s, 3H, CC**H**$_3$), 0.85 (t, *J* = 6.6 Hz, 3H, CHC**H**$_3$); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 172.3, 159.7, 136.5, 129.7 (2), 129.6, 128.3 (2), 121.5, 91.2, 59.0, 44.3, 38.8, 27.8, 22.6, 21.0, 15.0; HRMS (FAB+, M-Cl) exact mass calc'd for $(C_{17}H_{24}NO_2)^+$ requires *m/z* 274.1807, found *m/z* 274.1800. $[\alpha]_D$ = +17.0 (c = 0.12, MeOH). The stereochemistry of the title compound was confirmed by single crystal X-ray diffraction of crystals (*vide infra*) obtained from heating the salt into acetonitrile and allowing slow vapor diffusion in a toluene-filled chamber.

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[1] Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals;* 3rd ed., Pergamon Press, Oxford, 1988.

[2] Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978,** *43*, 2923.

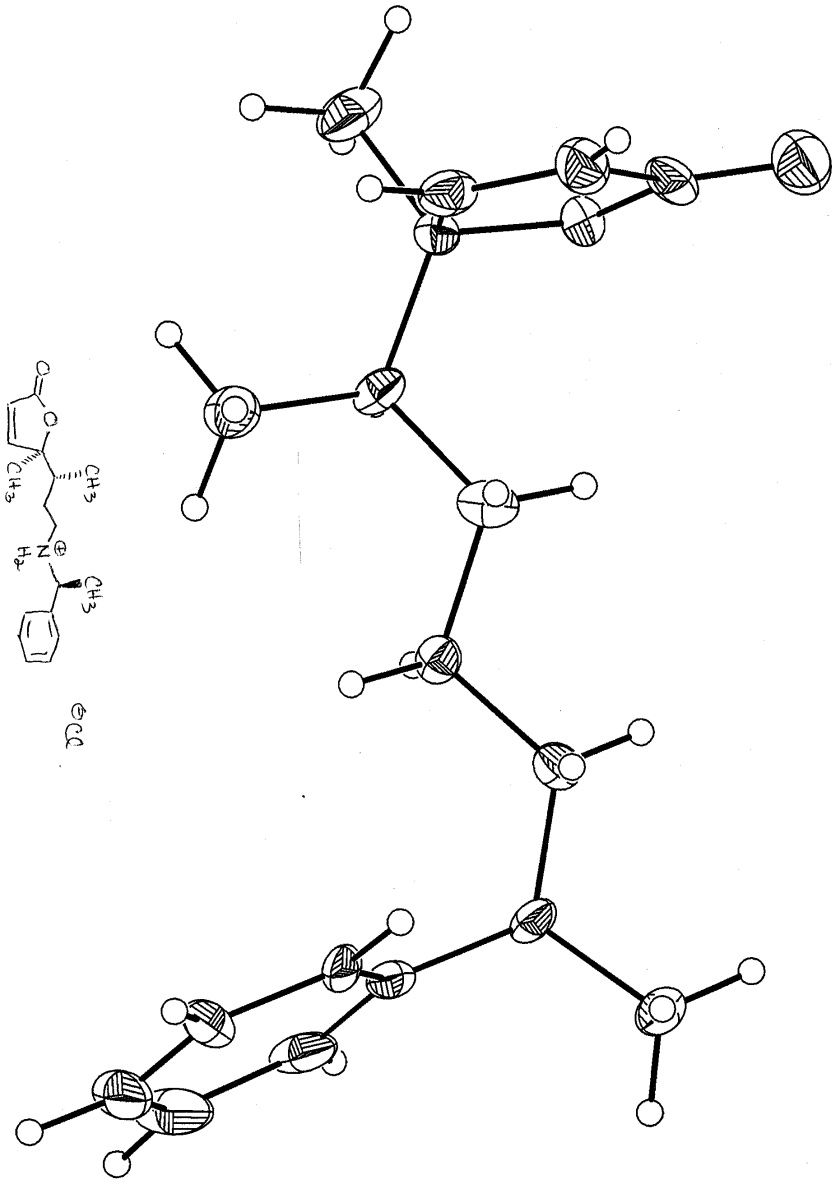
[3] Fujita, K.; Taka, H.; Oishi, A.; Ikeda, Y.; Taguchi, Y.; Fujie, K.;Saeki, T.; Sakuma, M. *Synlett* **2000**, 10, 1509.

[4] Torii, S.; Inokuchi, T.; Kondo, K. *Bull. Chem. Soc. Jpn.* **1983**, 56, 2183.

[5] Okazoe, T.; Takai, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 953.

[6] Martinez, A. G.; Alvarez, R. M.; Fraile, A. G.; Subramanian, L. R.; Hanack, M. *Synthesis.* **1987**, 49.; Martinez, A.G.; Alvarez, R. M.; Gonzalez, S. M.; Subramanian, L. R.; Conrad, M. *Tetrahedron Lett.* **1992**, *33*, 2043.

(5*R*,1'*R*)-5-Methyl-5-[1'-methyl-3'-((1*S*)-1-phenylethylamino)-propyl]-5*H*-furan-2-one hydrochloride



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LATT -1
SYMM 0.5-X, -Y, 0.5+Z
SYMM -X, 0.5+Y, 0.5-Z
SYMM 0.5+X, 0.5-Y, -Z
SFAC C  H  N  O  Cl
UNIT 68 92 4 8 4
L.S. 4
BOND $h
FMAP -2
PLAN 20
WGHT   0.060300   0.000000
FVAR   0.360920
TEMP -175
MOLE 1
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             0.037460   0.001080   0.002360 -0.001150
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             0.039160 -0.002740   0.002890 -0.000610
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0.022890 -0.000790 0.000780 -0.000680

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0.021610 -0.003240 0.002040 0.000480

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H0B 2 0.861953 0.604087 -0.003851 11.000000 -1.200000

AFIX 0

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AFIX 0

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H2B 2 0.504230 0.555769 0.051082 11.000000 -1.200000

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H5B 2 0.855276 0.613964 0.116591 11.000000 -1.200000

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AFIX 0

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AFIX 43

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H9 2 0.393368 0.408258 -0.099744 11.000000 -1.200000

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H10B 2 0.572932 0.413468 0.146442 11.000000 -1.500000

H10C 2 0.561451 0.438372 0.219336 11.000000 -1.500000

AFIX 0

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AFIX 43
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0.021190 -0.007010 -0.009840 0.028250

AFIX 43

H17 2 0.412741 0.209128 -0.110545 11.000000 -1.200000

AFIX 0

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Q2 1 0.806700 0.883500 0.988400 11.000000 0.050000 -0.54

Q3 1 0.540000 0.879000 0.994700 11.000000 0.050000 -0.51

Q4 1 0.740500 0.957400 0.996600 11.000000 0.050000 0.48

Q5 1 0.737600 0.807500 0.997500 11.000000 0.050000 0.44

Q6 1 0.601700 0.956300 0.990800 11.000000 0.050000 0.44

Q7 1 0.668100 0.920900 0.993200 11.000000 0.050000 -0.43

Q8 1 0.767800 0.879400 1.024600 11.000000 0.050000 -0.42

Q9 1 0.677300 0.883700 1.044500 11.000000 0.050000 -0.41

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Q11 1 0.674100 0.882000 0.971900 11.000000 0.050000 0.38

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Q13 1 0.459000 0.576900 0.001600 11.000000 0.050000 -0.38

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Q15	1	0.877900	0.598100	0.014400	11.000000	0.050000	-0.34
Q16	1	0.673000	0.663000	0.272500	11.000000	0.050000	-0.33
Q17	1	0.378000	0.519100	0.000800	11.000000	0.050000	0.33
Q18	1	0.730100	0.494900	-0.063600	11.000000	0.050000	0.31
Q19	1	0.520900	0.833900	0.957000	11.000000	0.050000	0.30
Q20	1	0.789800	0.620800	0.034900	11.000000	0.050000	-0.30

HKLF 4

END